SCIENTIFIC LETTER

Angiotensin II, but not aldosterone and renin, correlates positively with increased concentrations of N-terminal pro-brain natriuretic peptide in patients with chronic heart failure

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Activation of the renin–angiotensin–aldosterone system (RAAS) has a central role in the pathophysiology of congestive cardiac failure. Increased concentrations of RAAS neurohormones are associated with worse outcomes in patients with heart failure.[1] Blockade of this system with angiotensin converting enzyme (ACE) inhibitors, β blockers, and spironolactone is a cornerstone of treatment. Congestive cardiac failure is treated with a multiple drug approach limited by patient concordance, drug related side effects, and metabolic derangements. Despite chronic treatment RAAS activity can remain increased[1] and mortality of patients with congestive cardiac failure remains high.[2] Uncertainty concerning the combined role of ACE inhibitors and angiotensin II antagonists in heart failure has largely been resolved by the CHARM-Added (candesartan in heart failure assessment of reduction in mortality and morbidity for patients taking ACE inhibitors) study, which showed improvements in cardiovascular mortality and hospitalisations.[2] However, combination treatment in CHARM-Added did increase the risk of metabolic side effects. There may be a case for tailoring treatment for individual patients to maximise benefits.

Brain natriuretic peptide (BNP) concentrations are increased in congestive cardiac failure due to myocardial stretch and neuroendocrine interactions. BNP has potential for help in diagnosis and risk stratification.[3 4] We measured concentrations of and relations between RAAS neurohormones and N-terminal pro-BNP in patients with chronic heart failure.

METHODS

The study was approved by the local research ethics committee and informed consent was obtained from all patients. Fifty consecutive patients attending the St Mary's Hospital heart failure service were recruited. All patients had systolic dysfunction measured by transthoracic echocardiography. The causes of heart failure were coronary artery disease (70%, 35 patients), idiopathic (22%, 11 patients), alcohol (4%, 2 patients), and hypertension (4%, 2 patients). Seated blood pressure was recorded by sphygmomanometry and medication was recorded. Blood was taken for renin, aldosterone, angiotensin II, and N-terminal pro-BNP determinations. Patients were excluded if there had been an admission (within three months) for a myocardial infarction or heart failure decompensation; if they had moderate to severe renal impairment (creatinine $>$ 160 μmol/l); or if they were taking spironolactone.

Blood was drawn in the morning with the patients in a seated position, centrifuged (3000 rpm, 10 minutes), and stored at –40°C until analysis. Blood was frozen within 30 minutes of being drawn. Renin was measured by the ''active renin'' kit (Nichols Institute Diagnostics Ltd, San Clemente, California, USA); aldosterone was measured by the Diagnostics Products Corporation (Euro/DPC Ltd, Caernarfon, UK) ''Coat a Count'' assay; and angiotensin II was measured by a radioimmunoassay kit (Euro Diagnostica, Arnhem, the Netherlands). N-terminal pro-BNP was measured by an electrochemiluminescence immunoassay (Roche Diagnostics Corporation).

RESULTS

Results are expressed as mean (SEM). Regression was calculated by the least squares method.

Table 1 presents concentrations of renin, angiotensin II, aldosterone, and N-terminal pro-BNP according to drug treatment in the 50 patients (39 men, mean (SEM) age 68 (1) years). One patient excluded from table 1 was taking no medication on recruitment. This patient's neurohormonal profile was aldosterone 412 ng/l; renin 69 mU/l; and angiotensin II 6.0 pmol/l. Mean ejection fraction was 29 (2)%; New York Heart Association functional class 2.5 (1); blood pressure was 127 (3)/76 (1) mm Hg; and creatinine was 115 (4) μmol/l for all patients. These variables did not differ significantly between treatment groups.

There was a positive correlation between angiotensin II and aldosterone ($r = 0.4$, $p < 0.01$) but no significant relation between renin and angiotensin II or renin and aldosterone. N-terminal pro-BNP correlated significantly with angiotensin II ($r = 0.7$, $p < 0.01$) but not with renin or aldosterone.

DISCUSSION

We have shown, as previously reported, that patients with chronic heart failure have high concentrations of renin, angiotensin II, aldosterone, and N-terminal pro-BNP despite medical treatment, implying ongoing activation of RAAS.[1 3] Angiotensin II was still detectable despite treatment with β blockers (known to inhibit renin activity) and ACE inhibitors. Furthermore, renin and angiotensin II were not correlated, which may in part be due to ACE independent pathways for generation of angiotensin II. As expected from RAAS physiology we observed a significant relation between angiotensin II and aldosterone concentration as previously reported.[1] Continued activation of the RAAS, despite drug treatment, may have a role in the persistently high morbidity and mortality of patients with congestive cardiac failure.

N-terminal pro-BNP concentration is an independent predictor of mortality in patients with congestive cardiac

Abbreviations: ACE, angiotensin converting enzyme; BNP, brain natriuretic peptide; CHARM-Added, candesartan in heart failure assessment of reduction in mortality and morbidity for patients taking ACE inhibitors; RAAS, renin–angiotensin–aldosterone system

Table 1 Concentrations of renin, angiotensin II, aldosterone, and NT pro-BNP and their normal ranges in 50 patients with heart failure according to their treatment regimen

	Medication				
	Combined data (n = 50)	ACEI+/BB+ (n = 32)	ACEI+/BB− (n = 13)	ACEI−/BB+ (n = 4)	Normal range
Age (years)	68 (1)	67 (2)	70 (2)	70 (2)	
Renin (mU/l)	271 (149)	102 (25)	782 (553)	37 (14)	7–76
Angiotensin II (pmol/l)	12 (1)	10 (1)	12 (3)	14 (4)	19–38
Aldosterone (ng/l)	97 (10)	89 (8)	83 (14)	78 (14)	40–310
NT pro-BNP (pg/ml)	2552 (615)	1609 (419)	3889 (1710)	6333 (2334)	<227 (men <75 years) <334 (women <75 years)

Data are mean (SEM).
ACEI, angiotensin converting enzyme inhibitor; BB, β blocker; NT pro-BNP, N-terminal pro-brain natriuretic peptide.

failure.[3] The stimulus for BNP release is continuous myocyte overstretch, which promotes BNP synthesis by gene expression. In isolated human atrial and ventricular myocytes angiotensin II increased BNP gene expression and this was inhibited by losartan.[5] We have shown a strongly positive correlation between angiotensin II and BNP, which may reflect angiotensin II induced BNP gene expression in vivo. Long term treatment with angiotensin II antagonists reduces BNP concentrations in patients with heart failure.[3] Natriuretic peptides reduce RAAS activity by inhibiting secretion of renin and aldosterone. We did not find a negative relation between N-terminal pro-BNP and renin or aldosterone possibly due to loss of physiological regulatory mechanisms in chronic heart failure.

Chronic medical treatment of congestive cardiac failure is limited by long term concordance and side effects of polypharmacy, as well as having pharmacoeconomic implications. Some studies have shown use of angiotensin II antagonists added on to conventional ACE inhibition to be of benefit, although identifying patients who will gain most benefit is difficult. Some small studies have suggested that BNP concentrations may be used to select patients and guide the intensity of medical treatment.[4] Further studies are required to determine whether N-terminal pro-BNP concentrations can be used to target the use of angiotensin II antagonists to further block an active RAAS in appropriate patients.

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